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Good Clinical Practice Inspectors Working Group (GCP IWG)

ANNEX I
TO PROCEDURE FOR CONDUCTING GCP INSPECTIONS REQUESTED BY THE CHMP: INVESTIGATOR SITE

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1. Introduction

This annex compiles specific items that may be verified at the investigator site but their selection will depend on the scope of the inspection and can be established in the local inspection plan. Reference should be made to the Regulation (EU) No 536/2014, relevant GCP, national regulatory requirements and list of essential documents in determining the documentation, including electronic documents, which should be present and available for inspection. As the Regulation (EU) No 536/2014 provides the basis for the application of a risk proportionate approach to the design and conduct of clinical trials, inspectors should take this into account during the inspection when such an approach is implemented in the conduct of the clinical trial inspected. Risk adaptations should be clearly described and justified in a risk assessment and mitigation plan (see reference v for further information).

2. Legal and administrative aspects

The aim of the inspection is to determine if all legal and administrative aspects of the clinical trial have been accomplished.

The inspectors should check whether the authorisation of the clinical trial and its further modifications, the trial safety reporting and any other required authorisation/ notifications/ exchange of information have been carried out according to GCP principles, legal obligations and the applicable regulatory requirements.

In the case of EU investigator sites, the Member State decision on the authorisation of the trial and substantial modifications, as well as other clinical trial notifications and exchanges of information will be available from the EU clinical trial system for their further verification at the investigator site. The decision on the authorisation takes into consideration the ethical review by the ethics committee which shall be performed in line with the Member State legislation. Therefore inspectors should examine any specific Member State conditions related to the ethical review outlined in the decision that may require further verification at the site.

For sites outside the EU a separate ethical opinion from the authorisation of the trial may be required and available at the site for verification.

In both cases the following aspects should be considered, as applicable, for examination at the investigator site in relation to the ethics committee review:

- Identify the Independent Ethics Committee (IEC) for this site and check whether it provides a statement that it is organised and operates according to GCP and applicable laws and regulations. If applicable, verify the accreditation/ authorisation of the IEC by national authorities and the adequate composition and independence of the IEC according to national regulatory requirements[1].
- Determine whether IEC approval/ favourable opinion (signed and dated) was obtained before starting the trial and implementing any modifications at the centre and clearly identifies the trial, the investigator, the documents reviewed and their versions. The same has to be checked for modifications of the protocol and implementation of any urgent safety measures, if applicable.
- Determine whether the (coordinating) investigator or sponsor (when appropriate) has maintained copies of all reports submitted to the IEC, when the trial was initiated, and reports of all actions or modifications required prior to the approval/ favourable opinion and other notifications. If possible according to local regulations, check the necessary and available written operating procedures.

[1] Third country inspection should take into account national regulatory requirements, as applicable.

- Determine whether annual reports have been submitted to the IEC, if applicable.

It may be necessary to check any other required authorisation to perform the trial at the site and whether adequate information about the trial was given to other involved parties at the trial site (director of the institution, pharmacy, etc.). The documentation of insurance and indemnification should be checked.

3. Organisational aspects

3.1. Implementation of the trial at the site

Inspectors should examine the following elements:

Organisation and personnel:

- Organisation charts (facility management and scientific organisation charts).
- Documentation of delegation and acceptance of responsibilities by the principal investigator.
- Systems for QA and QC, if available.
- Standard Operating Procedure (SOP) system where available.
- Disaster plans, e.g. handling of defective equipment and consequences.
- Staff – qualification, responsibilities, experience, availability, training programmes, training records, CV.
- Numbers of clinical trials performed and their nature.
- Proportion of time allocated to clinical trial work.

The following points should be examined regarding the implementation of the study at the site:

- Contracts between the sponsor (or Contract Research Organisation (CRO)) and the investigator.
- Qualifications and experience of the investigator's team in the considered clinical area.
- Documentation describing the distribution of duties and functions for the conduct of the trial.
- Compatibility of the workload of the investigator and the staff with the requirements of the study.
- Organisation of the site for the study: organisation chart, GCP training, trial specific training, specific equipment, specific procedures.
- Regulatory authorisation to start the trial and supply the IMP.
- Compliance with the planned time schedule for the study.
- Correct and timely implementation of the correct versions of the protocol, informed consent form and amendments.
- First patient first visit (inclusion or selection) and last patient last visit.

3.2. Facilities and equipment

Inspectors should verify the proper use, adequacy and validation status of procedures and equipment used during the performance of the trial. A tour of the facilities can be considered, if applicable (e.g. the clinic, pharmacy, lab processing area). The following points should be examined:

- Equipment used.
- Equipment maintenance, service and calibrations.
- Facilities.
- Their suitability for the protocol requirements and the characteristics of the study being inspected.

For the conduct of the inspection at a laboratory site see Annex II and for phase I units see Annex V.

3.3. Management of biological samples

Inspectors should examine conditions and documentation regarding the management of biological samples, if applicable:

- Collection: person in charge of this task, dates and handling procedures, including labelling.
- Storage of the samples before analysis or shipping.
- Shipping conditions.

3.4. Organisation of the documentation

Inspectors should determine whether the general documentation and trial participants' documents (according to the guideline "GCP compliance in relation to the Trial Master File (TMF)" in Eudralex Volume 10, chapter V), is available, dated, signed and, if applicable, how it is archived at the trial site.

3.5. Monitoring and auditing

Points to consider, if available:

- The monitoring and follow-up by the sponsor: Number of visits at the site, scope and dates of the visits, content of the monitoring visit reports, where these have been requested from the sponsor, actions required by the monitor, monitoring visits log, monitoring plan and SOPs.
- Audit certificates (from sponsor file).

3.6. Use of computerised systems

The elements to be evaluated during an inspection of computerised systems used in clinical trials are established in a separate document (Annex III – computer systems). Computers may be study specific and supplied by the sponsor (eCRFs, ePRO, IRT). They may be site specific and part of the routine equipment of the site (medical records, on-line laboratory data, ECG recording, etc.).

4. Informed consent of trial participants

Inspectors should determine whether the informed consent was obtained in accordance with EU requirements as set out in in Chapter V of Regulation (EU) No 536/2014 and national regulatory requirements and guidelines in Eudralex Volume 10, by examining an appropriate sample of trial participants (including the trial participants whose medical records are reviewed), or the trial participants' legally acceptable representative, prior to their entry into the study. This needs to include patients whose medical records are reviewed.

Points to consider:

- The signed and self-dated (by the trial participant and by the person who conducted the informed consent discussion) consent form actually used and approved by the IEC at the time of inclusion of the trial participants.
- The information sheet actually used and approved by the IEC, in order to determine whether it includes all the elements requested by the EU requirements as set out in in Chapter V of Regulation (EU) No 536/2014, in Eudralex Volume 10 guidelines and in any national regulatory requirements[2].
- The centre practice for giving a copy of the informed consent to the patient.
- Consent for access to medical records by the authorities.
- Documentation in the source data of the process of obtaining the initial informed consent and subsequent consent to updates, including paediatric assent and emergency consent, if applicable.

5. Review of the trial participant data

Inspectors should check whether the investigator team conducted the clinical trial according to the approved protocol and its modifications by source data verification. In the source data verification it will be necessary to evaluate the source records taking into account their organisation, completeness and legibility. The description of the source data inspected can be reported by the inspector. It will be necessary to evaluate whether corrections of the data recorded in the case report form (CRF) was done according to the EU requirements as set out in Eudralex Volume 10 guidelines and the national regulatory requirements2 (signed and dated by the authorised person and providing justification, if necessary).

For a number of trial participants (the sample might include the first and last patient enrolled, etc.) the following points should be examined:

5.1. Characteristics of the trial participants included in the clinical trial

Inspectors should determine whether the inclusion of the trial participants in the trial was performed in accordance with the approved protocol and/or that protocol violations are documented, and also described in the study report.

Points to consider:

- Trial participants included in the clinical trial existed and participated in the clinical trial.
- Trial participants' participation was recorded in their medical records.
- Trial participants included fulfilled the inclusion criteria and none of the exclusion criteria stated in the protocol were present. Appropriate medical records must support these criteria.

[2] Third country inspection should take into account national regulatory requirements, as applicable.

5.2. Trial participants' visits calendar

Inspectors should determine whether the trial participants' visits calendar established in the protocol was followed. This check will include a review of the dates when the trial visits took place in order to evaluate whether they were done on the correct dates.

5.3. Efficacy and safety assessment data

Inspectors should verify whether the efficacy and safety data recorded in the CRF are in agreement with the source data obtained during the trial and whether adequate data management procedures were in place. Data related to endpoints should be compared with source documents, if appropriate, according to the scope of the inspection.

This check will also include whether adverse events recorded in the site records are also recorded in the CRF and were reported to the sponsor, IEC and authorities in accordance with the current regulations.

During the safety data verification, it will be necessary to evaluate the premature discontinuation of treatment and drop outs.

5.4. Concomitant therapy and intercurrent illness

Inspectors should verify whether concomitant therapy and intercurrent illnesses were managed in compliance with the protocol and recorded in the CRF and source documents.

6. Management of the Investigational Medicinal Product(s)

The aim is to verify whether all the activities related to the investigational medicinal product(s) have been conducted according to the protocol and other study documents.

Points to consider:

- Instructions for handling of investigational medicinal product(s) and trial related materials (if not included in protocol or investigator's brochure).
- Shipping records for investigational and unauthorised auxiliary medicinal product(s) and trial related material. Receipt date(s) of product delivery and quantity. This record should also contain batch numbers (check correspondence with the information kept at the sponsor site), expiration dates and codes assigned to the product and the trial participant.
- Visual appearance of IMP and comparators used, if still available at the site
- Documentation regarding allocation of treatment, randomisation and code breaking of investigational medicinal products.
- Investigational and unauthorised auxiliary medicinal product(s) accountability at site (pharmacy or investigator):
  - Date and quantity dispensed or returned, identification of recipients (patients' code or authorised person's). This record should contain also batch numbers, expiration dates and codes assigned to the product and the trial participant.
  - Documentation about re-labelling, if applicable.

  - Date and quantity returned to the sponsor. Return receipt: this record should also contain batch numbers, expiration dates and codes assigned to the product and the trial participant.

- Documentation of destruction of the investigational medicinal product (if destroyed at the site): dates and quantity. Documentation of receipt.
- Treatment compliance.
- Other activities, as appropriate:
  - Check the suitability of storage conditions and their records (fridge, freezer and controlled substances, etc.).
  - Review of the specific SOPs for this activity from the pharmacy or institution.
  - Check whether there was controlled access to the investigational medicinal product from receipt to dispensing.
  - Verification of the labelling for compliance with applicable requirements.

The inspectors should check that where required these documents have been signed and dated by the responsible persons according to the site and/or sponsor SOP and/or applicable requirements related to the management of the investigational medicinal products.

7. References

i. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

ii. Commission Implementing Act on Detailed arrangements for clinical trials inspection procedures including the qualifications and training requirements for inspectors, pursuant to Article 78(7) of Regulation (EU) No 536/2014.

iii. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use, as amended.

iv. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

v. Risk proportionate approaches in clinical trials. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use.

vi. EUDRALEX "Guidelines for Clinical Trials", Volume 10 of the Rules Governing Medicinal Products in the European Union.

vii. Annex II to Guidance for the conduct of GCP inspections – clinical laboratories.

viii. Annex III to Guidance for the conduct of GCP inspections – computer systems.

ix. Annex V to Guidance for the conduct of GCP inspections – phase I units.